DATA EVALUATION RECORD

ETHABOXAM
(LGC-30473)

STUDY TYPE: CHRONIC TOXICITY/CARCINOGENICITY FEEDING - RAT
[OPPTS 870.4300 (OECD 453)]
MRID 46387811/0902205

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Task Order: 103-2005

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DATA EVALUATION RECORD

STUDY TYPE: Combined Chronic Toxicity/Carcinogenicity Feeding - Rat [OPPTS 870.4300 [§83-5] OECD 453.

PC CODE: 090205 **DP BARCODE:** D313732

TEST MATERIAL (PURITY): Ethaboxam (LGC-30473, 99.0% a.i.)

SYNONYMS: *(RS)-N*-(α-cyano-2-thenyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5- carboxamide;

CITATION: Gardner, T., et al (2002) LGC-30473: Combined carcinogenicity and toxicity study by dietary administration to CD rats for 104 weeks. Huntingdon Life Sciences, Ltd. Wooley Road, Alconbury, Huntingdon, Cambridgeshire PE28 4HS England. Laboratory Report LKF002/984932. August 28, 2002. MRID 46387811. Unpublished

SPONSOR: LG Life Science, Ltd. Agrochemical Research Center, Yusong-gu, Daejon 305-380, Korea

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 46387811), Ethaboxam (LGC-30473, 99% a.i.) was administered in the diet to groups of 60 male and 60 female Crl:CD rats at concentrations of 0, 100, 300, or 650 ppm (approximately 0, 5.5, 16.4, or 35.8 mg/kg/day in males and 0, 7, 21, or 45.5 mg/kg/day, in females) for 104 weeks (carcinogenicity phase). Groups of 20 males and 20 females were administered the same diets and sacrificed at 52 weeks (chronic toxicity phase).

No treatment-related clinical signs, effects on survival/mortality, abnormalities of the eyes (ophthalmoscopic examination), hematologic changes, or urinalysis changes were observed in any group of male or female rats receiving any dose of the test material. No treatment-related neurological effects were observed during the functional observational battery (FOB). Statistically significant clinical chemistry changes were observed in male and female rats, but they were not considered adverse in the absence of corresponding histopathological lesions. Body weight gain was significantly decreased by 11% and 20% in mid- and high-dose males, respectively, and by 10%, 10%, and 17% in low-, mid-, and high-dose group females, respectively, during week 1 of the study; otherwise, there were no other treatment-related effects observed on body weight or body weight gain in males or low- or mid-dose females. High-dose group females weighed up to 12% less than controls throughout the remaining weeks of the study and gained 10% ($p \leq 0.01$) less weight than controls during the first year, 93% less during the

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second year, and 16% ($p \leq 0.05$) less over the entire study. Food consumption was within 8% of the control level throughout the study and food efficiency was similar to that of controls over the first 14 weeks of the study.

Organ weight changes, gross lesions, and microscopic lesions observed in male rats indicate that the male reproductive organs are targets for LGC-30473. No treatment-related changes in organ weights were observed in male rats at 52 weeks, but epididymal weight was significantly decreased in mid- and high-dose males and seminal vesicle weight was significantly decreased in high-dose group males compared with the control weights at 104 weeks. Gross examination showed an increased incidence of small testes in mid- and high-dose male rats at week 52, and significantly increased incidences of small, blue, or flaccid testes and small or flaccid epididymides in high-dose males in the carcinogenicity phase, compared with control incidences. The gross lesions corresponded with microscopic lesions observed in the testes and epididymides. The incidence of unilateral/bilateral seminiferous tubular atrophy in the testes was 6/18 ($p \leq 0.05$) in high-dose males and 6/20 ($p \leq 0.06$) in mid-dose males compared with 1/19 controls at 52 weeks. The incidence of abnormal spermatogenic cells in the epididymal duct was 7/18 ($p \leq 0.01$) in high-dose males and 0/19 in controls at 52 weeks. In the carcinogenicity phase, bilateral seminiferous tubular atrophy in the testes was observed in 41/60 ($p \leq 0.01$) high-dose males and 12/60 controls, but unilateral seminiferous tubular atrophy was observed in only 7/60 ($p<0.01$, negative trend) high-dose males and 23/60 controls. Degeneration of the seminiferous tubules in the testes was found in 3/60 (not statistically significant; N.S.) and 4/60 (N.S.) mid- and high-dose males, respectively, and 0/60 controls. The incidence of epididymides with no spermatozoa was 19/60 and 29/59 ($p \leq 0.01$) in mid- and high-dose males, respectively, compared with 9/59 in controls, and the incidence of epididymides with reduced number of spermatozoa was 18/59 ($p \leq 0.05$) in high-dose males compared with 8/59 in controls. Other epididymal lesions found at significantly increased incidences in high-dose males included abnormal spermatogenic cells and epithelial vacuolation in the epididymal duct and intraepithelial lumina. Microscopic lesions were also observed in the seminal vesicle and prostate. The incidence of seminal vesicle atrophy and acinar atrophy in the prostate was increased, but not significantly, in high-dose males and reduced colloid in the prostate was significantly increased in mid- and high group males. The non-neoplastic findings in male rats suggest that LGC-30473 is a potential endocrine disruptor affecting the male reproductive organs.

In female rats, no treatment-related lesions were observed at 52 weeks or in the carcinogenicity phase of the study. The incidences of lesions that were significantly increased at 52 weeks at the high dose (focal acinar cell atrophy and pituitary pars distalis hyperplasia) were not significantly increased in the carcinogenicity phase, and the incidence of ovaries with no corpora lutea was within range of historical controls.

The LOAEL for males is 300 ppm (16.4 mg/kg/day) based on effects in the male reproductive organs (testes, epididymides, prostate, and seminal vesicles) and the LOAEL for females is 650 ppm based on decreased body weight and body weight gain. The NOAEL for males is 100 ppm (5.5 mg/kg/day) and the NOAEL for females is 300 ppm (21.0 mg/kg/day).

At the doses tested, there was some evidence of carcinogenicity in male rats based on a significantly increased incidence of interstitial (Leydig) cell adenoma in the mid and high-dose

groups compared with the control group. The incidence was 1/60 (2%), 4/60 (7%), 6/60 (10%, p<0.05), and 7/60 (12%, p<0.05) at 0, 100, 300, and 650 ppm, respectively. The incidence of interstitial cell adenoma in the testes also exceeded that of historical controls, which ranged from 0-6.2% with an average of 2.5%. The test material produced non-neoplastic lesions in the testes, epididymides, seminal vesicles, and prostate and neoplastic lesions in the testes indicating that the mode of action of LGC-30473 is possibly endocrine disruption affecting the hypothalamic-pituitary-testicular axis in males.

The incidence of pituitary pars distalis adenoma was 32/60 (53%), 39/60 (65%), 43/60 (72%, p<0.01), and 36/60 (60%) and the incidence or pars distalis adenoma/adenocarcinoma combined was 42/60 (70%), 48/60 (80%), 51/60 (85%, p<0.05), and 51/60 (85%, p<0.05) in females at 0, 100, 300, and 650 ppm, respectively. The incidences of adenoma in mid-dose females and adenoma/adenocarcinoma combined in mid- and high-dose females were slightly above the upper range of historical controls; nevertheless, the lack of a clear dose-related trend and the extremely high incidence in controls suggest that the increased incidences are not treatment related. The rats were adequately dosed to test for carcinogenicity as evidenced by decreased body weight gain in female rats and non-neoplastic lesions in the reproductive organs in male rats.

The chronic toxicity/carcinogenicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement [OPPTS 870.4300); OECD 453] for a chronic toxicity/carcinogenicity study in rats. No deficiencies were noted that would affect the evaluation of this study.

Note: On February 15, 2006, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Ethaboxam. The CARC concluded (Memo, TXR No: 0054172) that there was a significant increasing trend, and a significant difference in pair-wise comparison of the 650 ppm dose group with the control for benign interstitial (Leydig) cell tumors of the testes, both at $p < 0.05$. It was also concluded that the pituitary tumors observed in female rats were not treatment-related.

COMPLIANCE: : Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:	LGC-30473
Description:	White powder
Lot/Batch #:	P980622
Purity:	99.0% a.i.
Compound Stability:	For duration of the study stored in the dark at 4°C
CAS # for TGAI:	162650-77-3

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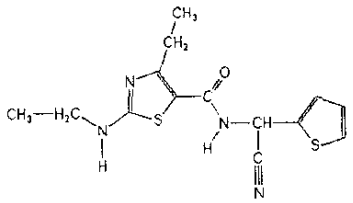
Structure:



2. **Vehicle and/or positive control:** The test material was administered in feed (SDS Rat and Mouse No. 1 diet). A positive control was not included in this study.

3. **Test animals:**

Species:	Rat
Strain:®BR	Crl:CD
Age/weight at study initiation:	5-6 weeks old: males: 141-202 g; females 122-173 g
Source:	Charles River (UK), Ltd., Margate, Kent, England
Housing:	Up to 5 of one sex housed together in suspended stainless steel cages with grid floors
Diet:	SDS Rat and Mouse No. 1 diet, *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions:	**Temperature:** 19-23°C **Humidity:** 40-70 % **Air changes:** not reported **Photoperiod:** 12 hours dark/12 hours light
Acclimation period:	13 days

B. STUDY DESIGN:

1. **In life dates:** Start: January 12, 1999; End: January 9-19, 2001

2. **Animal Assignment/Dose Levels:** Animals were assigned randomly to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Conc. in diet (ppm)	Dose to animal (mg/kg/day)		Main study (Carcinogenicity phase) 104 weeks		Interim sacrifice (Toxicity phase) 52 weeks	
		Male	Female	Male	Female	Male	Female
1 - Control	0	0	0	60	60	20	20
2 - Low (LDT)	100	5.5	7.0	60	60	20	20
3 - Mid (MDT)	300	16.4	21.0	60	60	20	20
4 - High (HDT)	650	35.8	45.5	60	60	20	20

Data taken from pages 19 and 34, MRID 46387811.

3. **Dose selection**: The dose levels were selected based on the results from a study (MRID 46387805) in rats administered the test material in feed at concentrations of 200, 650, or 2000 ppm for 13 weeks. Decreased testicular weight and gross testicular lesions were

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observed at necropsy. Severe testicular atrophy was observed at 2000 ppm and abnormal spermatids were observed at 650 ppm with associated changes in the epididymides.

4. **Diet preparation and analysis:** Diet was prepared weekly by grinding appropriate amounts of test substance with basal diet (SDS Rat and Mouse No. 1) and mixing in a Turbula mixer for at least 5 minutes to prepare a premix. The premix was diluted with basal diet to attain the desired concentration and mixed again in a Turbula mixer for 5 minutes to attain homogeneity of the dietary formulation. Homogeneity was tested on samples taken from the top, middle, and bottom of 30 ppm and 15,000 ppm dietary preparations and stability was tested on samples from the same dietary preparations. Samples were taken from the week 1 preparations and at 3-month intervals during the study for analysis of concentration.

Results:

Homogeneity analysis: The coefficient of variation was within 2% for the 30 ppm and 15,000 ppm dietary preparations.

Stability analysis: The mean concentration of test material found in the 30 ppm sample after storage for 8 days was 2% less than that of day 0; the mean concentration of the 15,000 ppm sample after storage for 8 days and both samples after storage for 22 days exceeded that of the day 0 concentration.

Concentration analysis: The mean concentration in the duplicate samples was within ± 9% of target concentrations for all dietary formulations. The test material was not detected in the basal diet.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Food consumption, body weight, clinical pathology, organ weight, and histopathology data: If 75% of all values were the same, a frequency analysis was applied to the data; treatment groups were compared using a Mantel test for trend and Fisher's exact test for pairwise comparisons. A parametric test was applied if analysis of homogeneity showed that Bartlett's test was not significant (1%); William's test was applied if the F1 test for monotonicity of dose-response was not significant (1%), or Dunnett's test was applied if the F1 test was significant (1%). If analysis of homogeneity showed that Bartlett's test was significant (1%), the data was subjected to a logarithmic or square-root transformation. If Bartlett's test was still significant, Shirley's test was applied if the H1 test for monotonoicity was not significant or Dunn's test was applied if the H1 test was significant. Histopathology data were analyzed using Fisher's exact test and mortality was analyzed using the log-rank method.

   For the neurobehavioral tests, data such as rearing and activity counts, grip strength, hindlimb landing footsplay, and rectal temperature were analyzed using one-way analysis of variance (ANOVA) followed by William's test. Categorical data such as ease of handling, arousal, etc. were analyzed using Jonckheere-Terpstra test (two-tailed except when responses were considered directional). The Coulbourn activity data were analyzed by ANOVA followed by Williams's test.

C. METHODS:

1. Observations:

1a. Cageside observations: Animals were inspected once a day during acclimation for signs of toxicity and twice a day for signs of toxicity and mortality during the treatment period.

1b. Clinical examinations: Clinical examinations with palpation were conducted weekly.

1c. Neurological evaluations: A functional observational battery (FOB) and motor activity assessment were conducted at about the same time each day between weeks 32 and 49. Ten male and ten female rats/group from the toxicity phase of the study were included in the FOB. The FOB consisted of three sets of observations: in the hand, in the arena, and manipulations. The weekly observations consisted of the initial handling followed by a brief (10 seconds) observation in the arena. A full FOB was conducted at weeks 32 and 49 and a short FOB (observations in the hand and in the arena) were conducted weekly from weeks 33-48. Motor activity also was assessed at weeks 32 and 49 using a Coulbourn Infra-red Activity Monitoring System. If all animals in all groups failed to show a given sign, this observation was not recorded in the summary tables in the study report. FOB testing was conducted prior to any laboratory investigations. The (X) parameters were evaluated.

	OBSERVATIONS IN THE HAND		MANIPULATIONS
X	Ease of removing from cage	X	Approach response
X	Reactivity to (ease of) handling	X	Touch response
X	Salivation/lacrimation	X	Auditory startle response
X	Exophthalmos	X	Righting reflex
X	Piloerection	X	Tail pinch response
X	Fur appearance	X	Pupil reflex
X	Vocalization on handling	X	Grip strength (forelimb)
		X	Grip strength (hindlimb)
	OBSERVATION IN THE ARENA	X	Landing foot splay
X	Convulsions, tremors, twitches	X	Body temperature (°C)
X	Activity counts	X	Body weight (g)
X	Level of arousal		
X	Rearing count		
X	Grooming		
X	Assessment of posture/gait		
X	Palpebral closure		
X	Presence of fecal boluses, urine		

2. **Body weight:** Animals were weighed 1 week before treatment, the first day of treatment, each week for the first 14 weeks, and at 4-week intervals thereafter.

3. **Food consumption and compound intake:** Food consumption for each cage of animals was measured starting 1 week before treatment (-1), weekly for the first 14 weeks of treatment, and at 4-week intervals thereafter. Mean daily diet consumption was calculated as g rat/week based on the number of surviving rats/cage and the total food consumption/cage or the total food consumed per week and the number of animal days for the group. Food efficiency was calculated as [body weight gain in g/food consumption in g per unit time] × 100 and compound intake (mg/kg/day) values were calculated from the consumption and body weight data.

4. **Ophthalmoscopic examination:** The eyes of all animals were examined with a binocular indirect ophthalmoscope before initiation of treatment, at week 51 on all control and 650 ppm group rats in the toxicity study, and at week 104 on 20 male and 20 female rats in the control and 650 ppm group rats (only 15 female rats in the 650 ppm group) in the carcinogenicity study. The pupils were dilated with a 1% tropicamide solution before the examination.

5. **Hematology & Clinical chemistry:** Blood was collected from the retroorbital sinus of all animals in toxicity study during weeks 13, 26, and 52 and 10 male and female rats/group in the carcinogenicity study at weeks 78 and 104. Blood was collected in EDTA for the hematologic evaluations, citrate for the coagulation tests, and lithium heparin for the clinical chemistry analyses. Food but not water was removed overnight before collection of blood. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)*
X	Platelet count*	-	Reticulocyte count
X	Blood clotting measurements*	X	Cell morphology
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		
X	(Activated partial thromboplastin time)		

* Recommended for combined chronic/carcinogenicity studies based on Guideline 870.4300.
- Not examined

b. Clinical chemistry:

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
-	Magnesium*	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*	-	Globulins*
X	Sodium*	X	Glucose (fasting)*
	ENZYMES (more than 2 hepatic enzymes)*	X	Total bilirubin
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
-	Cholinesterase (ChE)	-	Triglycerides
X	Creatine phosphokinase	X	A/G Ratio
-	Lactic acid dehydrogenase (LDH)		Serum protein electrophoresis
X	Alanine aminotransferase (ALT/ SGPT)*		
X	Aspartate aminotransferase (AST/ SGOT)*		
X	Gamma glutamyl transferase (GGT)*		
-	Sorbitol		
-	Glutamate dehydrogenase*		

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.
- Not examined

6. **Urinalysis:** Urine was collected overnight from the same animals sampled for blood; food and water were removed during urine collection. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity / osmolality*	X	Bilirubin*
X	pH*	X	Blood/ red blood cells*
X	Sediment (microscopic)	-	Nitrate
X	Protein*	-	Urobilinogen

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.
- Not examined

7. **Sacrifice and pathology**: All animals that died, those sacrificed moribund, and those sacrificed on schedule at week 52 or 104 were subjected to gross pathological examination. The rats were killed by carbon dioxide asphyxiation. The CHECKED (X) tissues, except for eyes and testes/epididymides, were collected and preserved in 10% neutral buffered formalin. Eyes were preserved in Davidson's fluid and testes/epididymides were preserved in Bouin's fixative followed by 70% industrial methylated spirits. All tissues and gross lesions from all control rats and 650 ppm group rats in the toxicity and carcinogenicity phase, and all 100- and 300 ppm group rats dying or killed moribund were examined microscopically. The kidneys, liver, lungs, testes, epididymides, and gross lesions from all 100 ppm and 300 ppm group rats were examined microscopically; prostate, seminal vesicles, coagulating, and female pituitary gland from rats in the 100 ppm and 300 ppm groups killed at 104 weeks also were examined microscoically. The (XX) organs, in addition, were weighed; the thyroid and parathyroids were weighed together.

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	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
-	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*	X	Peripheral .nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	XX	Thymus		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	-	Harderian gland
X	Rectum*	X	Urinary bladder*	XX	Parathyroids*
XX	Liver*+	XX	Testes*+	XX	Thyroids*
-	Gall bladder* (not rat)	XX	Epididymides*+	X	Mammary gland*
X	Bile duct (rat)	XX	Prostate*		
X	Pancreas*	XX	Seminal vesicle*		
	RESPIRATORY	XX	Ovaries*+		OTHER
X	Trachea*	XX	Uterus*+ with cervix	X	Bone (sternum and/or femur)
X	Lung*	X	Coagulating gland	X	Skeletal muscle
X	Nose*	X	Vagina	X	Skin*
X	Pharynx*			X	All gross lesions and masses*
X	Larynx*				
X	Head (nasal cavity, paranasal sinuses, nasopharynx				

* Required for combined chronic/carcinogenicity studies based on Guideline 870.4300.
+Organ weight required in combined chronic/carcinogenicity studies.
- Not examined

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity**: The incidences of clinical signs in treated rats were not statistically significantly different from those of the control groups. The report noted that an orange stain was observed consistently on the tray paper under the cage of rats in the mid-and high-dose groups during the first year of the study and intermittently during the second year. The stain was attributed to excretion of the parent compound or metabolite. Common observations included hair loss, hunched posture, encrustation on the tail, abnormal gait (females only), and brown stain on the lumbar region of the body.

2. **Mortality**: In the toxicity phase of the study, one control, two high-dose males, and one mid-dose female rat died before termination of this study at week 52. Table 2 summarizes the mortality/survival of male and female rats in the carcinogenicity phase. A sufficient number of male rats were alive at 18 months and study termination for evaluation of carcinogenicity. Survival was much lower among the groups of female rats than for male rats; however, the number of surviving female rats in all groups met the minimal requirement of 25% at study termination.

TABLE 2. Mortality/survival of male and female rats fed LGC-30473 - carcinogenicity study				
Time	Concentration (ppm)			
	0	100	300	650
	Males			
Week 0	60	60	60	60
Week 54	57 (95)[a]	56 (93)	59 (98)	58 (97)
Week 78	52 (87)	50 (83)	53 (88)	51 (85)
Week 104	30 (50)	30 (50)	35 (58)	31 (52)
Deaths during necropsy period	1	0	0	3
	Females			
Week 0	60	60	60	60
Week 54	57 (95)	56 (93)	56 (93)	59 (98)
Week 78	46 (77)	45 (75)	39 (65)	37 (62)
Week 104	21 (35)	15 (25)	15 (25)	15 (25)
Deaths during necropsy period	0	0	0	0

Data taken from page 31 and Table 1 (pp. 51-56), MRID 46387811.
[a]The numbers in parentheses are percent of initial number of animals assigned to the carcinogenicity study.

3. **Neurological evaluations:** Significantly ($p<0.05$) fewer high-dose than the control females vocalized during handling at the weekly evaluations. The greatest difference between high-dose and control females was observed at week 35 (1/10 high-dose vs 6/10 controls vocalized) and week 37 (1/10 high-dose vs 5/10 controls vocalized). At week 45, vocalization was observed in 3/10 high-dose males ($p<0.05$) compared with 0/10 controls; otherwise, no notable differences between high-dose and control males were observed. During week 33, 0/10 high-dose males ($p<0.05$) walked on their toes compared with 4/10 controls. No statistically significant differences between treated and control groups were observed for mean activity count, mean rearing count, mean forelimb grip strength, mean hindlimb grip strength (females only), hindlimb footsplay, body temperature, or locomotor activity. High-dose males had hindlimb grip strength 17% ($p\leq0.05$) less than that of the controls at week 32, but no significant difference was observed at the week 49 evaluation.

B. **BODY WEIGHT:** Selected mean body weight and weight gain data are presented in Table 3. The study authors did not calculate weekly body weight gain. Mean body weights of all groups of male rats and low- and mid-dose groups of female rats were similar to (within ± 8%) that of controls throughout the study. Mean body weight of high-dose female rats was similar to those of controls up to week 86 after which mean body weight was 12% less than that of controls. Mid- and high-dose males gained 11% ($p\leq0.01$) and 20% ($p\leq0.01$) less weight than controls during the first week of treatment, and low- and mid-dose females gained 10% ($p\leq0.01$) less weight than controls and the high-dose females gained 17% ($p\leq0.01$) less weight than controls. After week 1, male rats showed no treatment-related effect on weight gain at any dose level, but the low- and high-dose groups lost more weight than controls from weeks 78-104. High-dose females gained 14-15% less weight than controls from weeks 13 to 50 and weeks 50-78, 93% less from week 78-104, and 16% less for the entire study. Weight gain by low- and mid-dose females was similar to or slightly

greater than that of controls throughout the study except during the 78-104 week intervals where they lost weight and controls gained weight.

TABLE 3: Selected mean body weight and weight gain in male and female rats fed LGC-30473 for up to 2 years

Week of study	Dietary concentration (ppm)							
	0	100	300	650	0	100	300	650
	Males				Females			
Body weight (g)								
0	173.3	173.2	175.3	175.6	145.9	144.0	145.8	146.2
1	227.9	226.3	224.7	219.7	176.0	171.3	173.0	171.1
13	533.7	531.5	533.5	519.5	291.5	287.3	293.0	279.9 (96)[a]
50	721.6	735.8	734.6	718.9	444.3	434.1	433.3	410.9 (92)
52 (T)[b]	696.9	718.1	723.8	688.2	424.1	421.4	412.8	408.1 (96)
78	793.8	805.3	814.1	789.3	522.0	517.9	531.5	477.2 (91)
104	781.9	770.3	818.0	730.5 (93)	544.1	502.7	520.6	478.7 (88)
Body weight gain (g)								
0-1	55	53	49** (89)	44** (80)	30	27** (90)	27** (90)	25** (83)
0-13[c]	360.4	358.2	358.2	343.9	145.6	143.3	147.2	133.7
13-50[c]	187.9	204.3	201.1	199.4	152.8	146.8	140.3	131.0 (86)
1-50	494	510	510	500	268	263	260	240** (90)
50-78[c]	72.2	69.5	79.5	70.4	77.7	83.8	98.2	66.3 (85)
78-104[c]	-11.9	-35.0	3.9	-58.8	22.1	-15.2	-10.9	1.5 (7)
50-104[c]	60.3	34.5	83.4	11.6	99.8	68.6	87.3	67.8 (68)
0-104[c]	609	599	643	558 (92)	397	357	374	332* (84)
Food consumption (g/rat)								
1	192	187	182** (95)	177** (92)	144	138* (96)	136** (94)	134** (93)
2-50	9802	9728	9740	9540* (97)	7437	7379	7389	7095** (95)
1-104[d]	7447	7275	7369	7134** (96)	5878	5802	5842	5584** (95)
Food conversion efficiency (%)								
1	28.5	28.3	27.1	25.0 (88)	20.8	19.7	20.0	18.6 (89)
1-14	13.3	13.3	13.3	13.2	7.4	7.4	7.6	7.1

Data obtained from Tables 3, 4, and 5 (pp.75-79), MRID 46387811.
Statistical analysis was not performed on mean body weight
[a]Numbers in parentheses are percent of control calculated by the reviewer.
[b]Terminal body weight for animals at 52 weeks (toxicity phase).
[c]Body weight gain calculated by the reviewer using mean body weight data.
[d]Includes animals in the carcinogenicity phase only.
*p≤0.05, **p≤0.01, Statistically significant, treated group compared with controls.
Note: Statistical Analysis on mean BW was not performed.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption data are summarized in Table 3. Mid- and high-dose group males and low-, mid-, and high-dose group females consumed significantly less (5-8%)

food than controls during the first week of the study. The total amount of food consumed by high-dose group male and female rats from weeks 2-50 and 1-104 was significantly (males $p \leq 0.5$, respectively; females, $p \leq 0.01$) less than that of controls; the reduction was only 3-6% less than that of controls for males and 5-6% less for females. Food consumption over the entire study for low- and mid-dose group male and female rats was similar to that of controls.

2. **Compound consumption:** Average compound intake for the entire study is summarized in Table 1.

3. **Food efficiency:** Food conversion efficiency values for high-dose group male and female rats were 12% and 11% less, respectively, than that of controls for week 1 of the study. Otherwise food efficiency was similar for the treated and control groups from weeks 2-14 of the study (Table 3).

D. OPHTHALMOSCOPIC EXAMINATION: No treatment-related ophthalmoscopic findings were observed in male or female rats receiving any dose of the test material. The report noted that a slightly greater number of high-dose male and female rats had a faint posterior suture line opacity at study termination (week 104); this finding was considered incidental.

E. BLOOD ANALYSES:

1. **Hematology:** No treatment-related effects were observed on any hematologic parameter in male or female rats receiving any dose of the test material. Statistically significant differences were observed for various parameters, but none showed dose- or time-related trends. The magnitude of the differences was generally small compared with controls.

2. **Clinical chemistry:** Notable clinical chemistry parameters are presented in Table 4. Female rats had changes in total protein, A/G ratio, total cholesterol, and glucose levels during the first year of the study. Total protein was significantly increased by 5-8% ($p \leq 0.01$) in the mid- and high-dose group females at weeks 13 and 52 compared with that of controls; no clear dose related trend was observed. The A/G ratio was significantly decreased by 4-7% ($p \leq 0.01$ or ≤ 0.05) in the mid- and high-dose group females at weeks 13 and 26, and in the high-dose group at week 52 suggesting that the increase in total protein was due to an increase in globulin, since no significant change was observed in the albumin level. High-dose group male rats had 4% ($p \leq 0.01$) and 9% ($p \leq 0.05$) increases in total protein at weeks 13 and 78, respectively, compared with those of controls; there was a 3% ($p \leq 0.05$) increase in albumin at week 13.

   Total cholesterol levels were significantly ($p \leq 0.01$ or ≤ 0.05) elevated by 25-35% in high-dose group females at weeks 13, 25, and 52, by 19% and 32% in mid-dose females at weeks 13 and 52, and by 21% in low-dose females at week 52 compared with the control levels. The total cholesterol level was significantly elevated (26%, $p \leq 0.01$) in high-dose males only at week 13. The glucose levels were significantly ($p \leq 0.01$ or ≤ 0.05) elevated by 13-19% in the high-dose group females at weeks 13, 52, and 78 compared with those of controls and by 10-13% in the low- and mid-dose groups at weeks 13 and 52. The glucose level at study termination was significantly decreased by 17% ($p \leq 0.05$) in high-dose females compared

with that of controls. The glucose level in high-dose male rats was significantly affected only at week 52, with the level 22% above that of controls. Creatine phosphokinase (CPK) activity was significantly decreased in all treated male groups at week 26, in mid- and high-dose group males at week 78, and in all treated female groups at week 78 compared with controls.

Electrolyte levels were significantly elevated in male and female rats in all dose groups compared with those of the controls during some phases of the study (Table 3). Generally, the changes were small (within ± 5% of the control levels except potassium in high-dose males and calcium in mid-dose females), transient, sporadic, inconsistent between the sexes, and had no pathologic correlates.

TABLE 4. Selected clinical chemistry changes in male and female rats fed LGC-30473								
	Dietary concentrations							
	Males				Females			
	0	100	300	650	0	100	300	650
13 Weeks								
T. Prot. (g/L)	67 ± 3.1[a]	68 ± 2.4	68 ± 4.3	70 ± 3.3** (104)[b]	78 ± 5.0	81 ± 5.0	84 ± 5.1** (108)	82 ± 4.5** (105)
Alb. (g/L)	30 ± 0.8	31 ± 1.1	31 ± 1.7	31 ± 1.0* (103)	40 ± 3.5	42 ± 2.4	42 ± 2.9	41 ± 2.3
A/G ratio	0.83 ± 0.05	0.83 ± 0.05	0.83 ± 0.05	0.81 ± 0.06	1.05 ± 0.09	1.05 ± 0.56	1.01 ± 0.56** (96)	1.00 ± 0.40** (95)
T. Chol (mmol/L)	1.97 ± 0.25	1.94 ± 0.40	2.09 ± 0.50	2.49 ± 0.56** (126)	2.95 ± 0.49	3.31 ± 0.86	3.50 ± 0.59* (119)	3.68 ± 0.64** (125)
Gluc. (mmol/L)	6.21 ± 0.60	5.80 ± 0.67	5.75 ± 0.77	6.23 ± 0.83	5.30 ± 0.74	5.83 ± 0.77* (110)	5.90 ± 0.68** (111)	6.04 ± 0.51** (114)
Na (mmol/L)	144 ± 0.7	144 ± 0.8	144 ± 1.2	145 ± 1.0** (101)	144 ± 1.4	145 ± 1.4	146 ± 1.5** (101)	147 ± 1.1** (102)
Cl (mmol/L)	103 ± 0.9	103 ± 1.3	102 ± 1.2	103 ± 1.2	102 ± 1.4	103 ± 1.4	103 ± 1.1** (101)	105 ± 1.5** (103)
26 Weeks								
T. Prot. (g/L)	70 ± 3.0	70 ± 2.7	70 ± 4.1	70 ± 2.6	79 ± 3.8	81 ± 4.3	81 ± 4.8	81 ± 3.2
Alb. (g/L)	31 ± 0.8	31 ± 1.0	30 ± 1.5	31 ± 0.9	39 ± 2.5	40 ± 1.9	39 ± 3.0	39 ± 2.3
A/G ratio	0.79 ± 0.04	0.79 ± 0.04	0.78 ± 0.05	0.78 ± 0.04	0.98 ± 0.07	0.97 ± 0.05	0.94 ± 0.06* (96)	0.93 ± 0.05** (95)
T. Chol (mmol/L)	2.26 ± 0.36	2.23 ± 0.50	2.22 ± 0.61	2.55 ± 0.55	3.11 ± 0.50	3.46 ± 0.95	3.54 ± 0.64	3.89 ± 0.70** (125)
Gluc. (mmol/L)	7.08 ± 0.91	6.89 ± 0.68	6.72 ± 0.78	7.01 ± 0.79	6.93 ± 0.94	6.82 ± 0.79	6.73 ± 0.77	7.19 ± 0.76
CPK (U/L)	217 ± 141.6	143 ± 56.1* (66)	147 ± 87.5* (68)	125 ± 67.5** (58)	95 ± 20.6	132 ± 76.0	118 ± 58.9	122 ± 43.3
Cl (mmol/L)	103 ± 0.9	102 ± 0.9	101 ± 1.1** (98)	101 ± 0.8 (98)	100 ± 1.6	98 ± 1.4** (98)	97 ± 1.7** (97)	97 ± 1.2** (97)
Ca (mmol/L)	2.71 ± 0.07	2.67 ± 0.07	2.65 ± 0.10* (98)	2.63 ± 0.08** (97)	2.78 ± 0.07	2.82 ± 0.10	2.83 ± 0.11	2.80 ± 0.10
52 Weeks								
T. Prot. (g/L)	71 ± 2.6	71 ± 2.8	70 ± 4.4	72 ± 2.9	74 ± 4.1	76 ± 5.8	80 ± 3.5** (108)	80 ± 4.5** (108)
Alb. (g/L)	30 ± 1.0	30 ± 1.4	30 ± 1.7	30 ± 1.5	35 ± 2.0	36 ± 3.1	37 ± 2.6	36 ± 3.1
A/G ratio	0.73 ± 0.05	0.72 ± 0.06	0.73 ± 0.06	0.72 ± 0.07	0.90 ± 0.08	0.89 ± 0.06	0.86 ± 0.09	0.84 ± 0.07* (93)
T. Chol (mmol/L)	2.59 ± 0.58	2.56 ± 0.71	2.49 ± 0.89	2.72 ± 0.60	2.67 ± 0.51	3.24 ± 1.05* (121)	3.53 ± 0.98** (132)	3.60 ± 0.88** (135)
Gluc. (mmol/L)	6.69 ± 1.10	7.19 ± 0.92	7.33 ± 1.25	8.13 ± 1.10** (122)	6.53 ± 0.65	7.23 ± 0.92* (111)	7.37 ± 0.90** (113)	7.36 ± 1.02** (113)
Na (mmol/L)	140 ± 1.0	141 ± 0.9	141 ± 0.9	142 ± 1.2** (101)	139 ± 1.2	140 ± 1.3* (101)	142 ± 1.6** (102)	143 ± 1.7** (103)
Cl (mmol/L)	104 ± 1.6	106 ± 1.1** (101)	106 ± 1.3** (102)	108 ± 1.1** (104)	105 ± 1.7	105 ± 1.3	106 ± 2.0	107 ± 2.4** (102)
Ca (mmol/L)	2.74 ± 0.07	2.70 ± 0.08	2.68 ± 0.12* (98)	2.65 ± 0.10** (97)	2.78 ± 0.07	2.89 ± 0.08** (104)	2.94 ± 0.10** (106)	2.81 ± 0.47** (101)
K (mmol/L)	3.7 ± 0.33	3.9 ± 0.17* (105)	3.9 ± 0.19* (105)	4.2 ± 0.28** (114)	3.6 ± 0.27	3.5 ± 0.34	3.5 ± 0.22	3.5 ± 0.29

	Dietary concentrations							
	Males				Females			
	0	100	300	650	0	100	300	650
78 Weeks								
T. Prot. (g/L)	65 ± 6.7	71 ± 4.0* (109)	70 ± 3.2* (108)	71 ± 2.3* (109)	77 ± 3.9	76 ± 4.6	78 ± 4.0	79 ± 3.7
Alb. (g/L)	31 ± 3.3	30 ± 10.6	33 ± 1.3	33 ± 1.2	38 ± 2.1	38 ± 2.0	39 ± 2.2	39 ± 3.0
A/G ratio	0.94 ± 0.04	0.81 ± 0.33	0.89 ± 0.04	0.90 ± 0.08	0.97 ± 0.08	1.02 ± 0.07	1.03 ± 0.08	0.98 ± 0.10
T. Chol (mmol/L)	2.86 ± 0.38	2.99 ± 0.66	3.04 ± 0.50	3.44 ± 0.99	3.30 ± 0.71	3.28 ± 0.94	3.26 ± 0.72	3.69 ± 1.25
Gluc. (mmol/L)	7.29 ± 1.81	6.05 ± 1.72	6.77 ± 0.84	6.23 ± 0.85	6.24 ± 1.52	6.36 ± 0.52	6.68 ± 0.79	7.44 ± 1.33* (119)
CPK (U/L)	432 ± 321.2	312 ± 160.8	188 ± 92.5* (44)	279 ± 116.8* (65)	162 ± 55.9	103 ± 23.7** (64)	115 ± 31.6** (71)	126 ± 28.1** (78)
Na (mmol/L)	140 ± 1.6	140 ± 1.3	140 ± 1.1	141 ± 1.1	138 ± 1.3	139 ± 1.3* (101)	140 ± 1.7* (101)	140 ± 1.9* (101)
Cl (mmol/L)	102 ± 2.2	102 ± 1.3	102 ± 1.1	104 ± 1.6	99 ± 2.9	101 ± 2.5* (102)	102 ± 2.3* (103)	103 ± 2.4** (104)
104 Weeks								
T. Prot. (g/L)	72 ± 4.6	69 ± 3.7	70 ± 2.5	70 ± 2.6	73 ± 4.3	73 ± 4.6	73 ± 3.7	74 ± 4.0
Alb. (g/L)	33 ± 2.6	33 ± 1.1	33 ± 1.1	33 ± 2.4	37 ± 3.0	38 ± 2.5	37 ± 2.6	38 ± 2.3
A/G ratio	0.83 ± 0.08	0.89 ± 0.08	0.90 ± 0.06	0.89 ± 0.11	1.01 ± 0.12	1.10 ± 0.05	1.04 ± 0.13	1.03 ± 0.07
T. Chol (mmol/L)	3.61 ± 1.31	3.25 ± 0.69	3.90 ± 0.93	3.95 ± 1.66	3.37 ± 0.92	3.43 ± 1.10	3.44 ± 0.79	3.98 ± 1.22
Gluc. (mmol/L)	5.44 ± 1.46	5.73 ± 1.05	6.00 ± 0.47	5.06 ± 1.02	6.48 ± 1.07	5.54 ± 0.94	5.99 ± 1.23	5.37 ± 1.33* (83)
Bili. (μmol/L)	2 ± 1.5	2 ± 1.2	2 ± 0.7	2 ± 1.2	1 ± 0.8	2 ± 1.* (200)	2 ± 0.6* (200)	2 ± 0.7* (200)
Na (mmol/L)	140 ± 1.2	140 ± 1.0	141 ± 1.0	142 ± 2.3** (101)	141 ± 1.5	140 ± 1.5	139 ± 1.3* (99)	140 ± 2.1* (99)
Cl (mmol/L)	101 ± 2.8	102 ± 1.8	102 ± 1.5	103 ± 3.2	102 ± 1.8	98 ± 3.2* (96)	99 ± 3.2* (97)	98 ± 3.9* (96)

Data taken from Table 8 (pp. 103-122), MRID 46387811.
[a]Mean ± standard deviation
[b]Numbers in parentheses are percent of control calculated by the reviewer.
*p≤0.05; **p≤0.01, statistically significant, treated group compared with the control group.

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F. **URINALYSIS:** Volume, pH, specific gravity, and protein content were not adversely affected in male or female rats receiving any dose of the test material. The pH was slightly increased in males at all doses at week 13; a dose-related trend was not observed indicating that the pH change was not treatment related. Urine volume was significantly increased (+52%, $p \leq 0.05$) and specific gravity was decreased (-1%, $p \leq 0.05$) at week 13 in mid-dose group female rats compared with control values; urine pH was decreased in the low-dose group at week 52. No other statistically significant changes in urinalysis parameters were observed in male or female rats receiving any dose of the test material.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Selected organ weights are presented in Table 5. At week 52, organ weights of treated male rats were similar to those of the control group. Kidney weight in mid- and high-dose female rats was significantly increased (11 and 7%, respectively, $p \leq 0.01$) and uterus+cervix weight of high-dose females was significantly increased (25%, $p \leq 0.05$) at week 52 compared with the control group. At week 104, the epididymis weight of mid- and high-dose group males was 12% ($p \leq 0.05$) and 25% ($p \leq 0.01$) less, respectively, than that of the control group. Additionally, seminal vesicle weight of high-dose male rats was 17% ($p \leq 0.05$) less than that of the control group. Organ weights of treated female rats were similar to those of controls at 104 weeks.

TABLE 5. Selected organ weights of male and female rats fed LGC-30473

Organ	Dietary concentration (ppm)			
	0	100	300	650
	Females - 52 weeks			
Terminal BW (g)	424.1 ± 81.6[a]	421.4 ± 74.7	412.8 ± 70.2	408.1 ± 48.5
Kidneys (g)	2.85 ± 0.35	2.98 ± 0.52	3.15 ± 0.57** (111)[b]	304 ± 0.27** (107)
Uterus+cervix (g)	0.606 ± 0.139	0.692 ± 0.177	0.677 ± 0.142	0.755 ± 0.307* (125)
	Males - 104 weeks			
Terminal BW (g)	774.1 ± 132.5	758.9 ± 137.3	810.5 ± 99.2	716.7 ± 123.2
Epididymides (g)	1.392 ± 0.285	1.298 ± 0.266	1.226 ± 0.197* (88)	1.046 ± 0.284** (75)
Seminal vesicle (g)	2.031 ± 0.914	1.598 ± 0.594	1.585 ± 0.543	1.695 ± 1.817* (83)

Data taken from Table 10 (pp. 133-144), MRID 46387811.
[a]Mean ±standard deviation
[b]Numbers in parentheses are percent of control calculated by the reviewer.

2. **Gross pathology:** The incidences of notable gross lesions are presented in Table 6. Small testes were observed in three male rats each in the mid- and high-dose groups compared with none of the control group at week 52 (toxicity phase). In the carcinogenicity phase, increased incidences of gross lesions in the epididymides and testes were observed in treated males. The incidences of small (30%) or flaccid epididymides (22%) were significantly increased in the high-dose group males compared with those of controls (10% and 8%, respectively). The incidences of small, blue, and flaccid testes also were significantly ($p \leq 0.01$ or ≤ 0.05) increased in high-dose male rats (48%, 52%, and 28%, respectively) compared with controls (12%, 23%, and 10%, respectively). Testicular masses were observed in 8% and 10% ($p \leq 0.05$ for both) of mid- and high-dose male rats compared with

0% for the controls. Brain depression from a pituitary mass in females occurred in a significantly larger number of high-dose female rats (77%) compared with a high background incidence (52%) for the controls. This lesion is related to pituitary tumors that occurred at a high incidence in all groups of female rats. Other gross lesions that occurred at significantly increased incidences in low or mid- dose rats were considered incidental, because no significant increase was observed in the high-dose group.

TABLE 6. Notable gross lesions in male and female rats fed LGC-30473 for up to 104 weeks

Organ/Lesion	Dietary Concentration (ppm)			
	0	100	300	650
Males – Toxicity study – 52 weeks[a]				
No. animals examined	19	20	20	18
Testes Small	0	1 (5.0)[b]	3 (15.0)	3 (15.0)
Males – Carcinogenicity Study				
No animals examined	60	60	60	60
Epididymides Small Flaccid	 6 (10.0) 5 (8.3)	 4 (6.7) 4(6.7)	 8 (13.3) 5 (8.3)	 18 (30.0)** 13 (21.7)*
Testes Small Blue Flaccid Mass(es)	 7 (11.7) 14 (23.3) 6 (10.0) 0 (0.0)	 6 (10.0) 7 (11.7) 7 (11.7) 3 (5.0)	 14 (23.3) 16 (26.7) 10 (16.7) 5 (8.3)*	 29 (48.3)** 31 (51.7)** 17 (28.3)** 6 (10.0)*
Females – Carcinogenicity Study				
No. animals examined	60	60	60	60
Brain Depression from pituitary mass	 31 (51.7)	 37 (61.7)	 40 (66.7)	 46 (76.7)**

Data taken from Table 11 (pp. 145-175), MRID 46387811.
[a]Animals in the toxicity study that died before week 52 were excluded from the summary table.
[b]Numbers in parentheses are percent of affected animals in the group calculated by the reviewer.
*$p \leq 0.05$, **$p \leq 0.01$, statistically significant, treated group compared with the control, calculated by the reviewer.

3. Microscopic pathology:

a. **Non-neoplastic:** Notable non-neoplastic lesions in male and female rats fed the test material are presented in Table 7. In the 52-week toxicity phase of the study, 35% ($p<0.01$) of high-dose male rats had abnormal spermatogenic cells in the duct of the epididymis compared with none of the controls. Abnormal spermatogenic cells also were observed in three and four male rats in the low- and mid-dose groups, respectively. There was no clear dose-related increase in severity of the epididymal lesion in male rats. The incidences of other lesions in the epididymis of treated male rats were not significantly increased in the toxicity phase. Bilateral seminiferous tubular atrophy was observed in 15, 20, and 28% (N.S.) of males in the low-, mid-, and high-dose groups, respectively, compared with only 5% of controls. The incidence of unilateral + bilateral seminiferous tubular atrophy was marginally increased in mid- and high-dose group male rats. The increased incidence of lesions in the testes and epididymides indicate that the male reproductive organs are targets of the test material. Generalized hepatocyte hypertrophy

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was observed in two high-dose males and centrilobular hepatocyte hypertrophy was observed in one high-dose male compared with none of the controls (not listed in the Table 7). The high-dose group female rats in the toxicity study had significantly increased incidences of focal acinar cell atrophy in the pancreas (35%, $p<0.01$) and hyperplasia in the pars distalis of the pituitary (30%, $p<0.05$) compared with 0% in the control group for both lesions. The incidence of ovaries with no corpora lutea also was significantly increased in high-dose group females (40%, $p<0.05$) compared with that of controls (10%). No other notable histopathological lesions were observed in the toxicity phase.

In the carcinogenicity phase of the study, male rats had increased incidences of lesions in the testes, epididymides, prostate, and seminal vesicles. The incidence of bilateral seminiferous tubular atrophy in the testes was significantly increased in high-dose male rats (68% vs 20% for controls, $p<0.01$). In contrast, significantly fewer high-dose male rats (12%, $p\leq0.01$) had unilateral seminiferous tubular atrophy compared with controls (38%). The incidence of bilateral seminiferous tubular atrophy was not significantly increased in low- and mid-dose group rats, but the average severity of the lesion was greater in all treated groups than in the controls. The incidence of unilateral + bilateral seminiferous tubular atrophy also was significantly increased in high-dose male rats compared with that of controls. Seminiferous tubular degeneration was observed in one low-dose, three mid-dose, and four high-dose male rats compared with none of the controls; the incidence was not significantly increased but showed a positive dose-related trend. High-dose male rats also had significantly increased ($p<0.01$ or <0.05) incidences of epididymal lesions: absent or reduced number of spermatozoa, abnormal spermatogenic cells in the duct, epithelial vacuolation in the duct, and intraepithelial lumina. The incidences of these lesions in the high-dose group ranged from 31% to 49% except for abnormal spermatogenic cells, which was 78%; the control incidences were 14-17% and 34% for abnormal spermatogenic cells in the duct. The incidence of absent epididymal spermatozoa in mid-dose males was 32% ($p<0.01$) compared with 15% for the control group. The total incidence of absent and reduced number of epididymal spermatozoa combined in mid- and high-dose male rats was 47% ($p<0.05$) and 80% ($p<0.01$), respectively, compared with 29% for the controls. The average severity of abnormal spermatogenic cells in the duct showed a clear dose-related trend. Although the average severity of reduced number of epididymal spermatozoa was increased at the high-dose, a clear trend was not observed for this lesion. High-dose group male rats also had increased incidences of acinar atrophy (N.S.) and reduced colloid ($p<0.05$) in the prostate and seminal vesicle atrophy (N.S.). Mid-dose group male rats also had an increased incidence of reduced colloid in the prostate ($p<0.01$).

Female rats in the carcinogenicity study had increased incidences of brain depression due to an enlarged pituitary and absent corpora lutea in the ovaries at all doses compared with control incidences. The incidence of the ovarian finding was within range of historical controls and the brain depression was due to pituitary tumors that were found in a large number of females in all groups. Therefore, these lesions are not considered treatment related.

TABLE 7. Notable non-neoplastic lesions in male and female rats receiving S-1812 for up to 104 weeks

Organ/Lesion	Dietary concentration (ppm)			
	0	100	300	650
Males – Toxicity study – 52 weeks[a]				
Epididymides [No. examined]	[19]	[20]	[20]	[18]
No spermatozoa	0	0	1	0
Reduced no. spermatozoa	1	2	1	3
Abnormal spermatogenic cells in duct	0	3 (1.67)[b]	4 (2.00)	7** (1.86)
Epithelial vacuolation in duct	4	7	6	7
Intraepithelial lumina	0	0	1	2
Testes [No. examined]	[19]	[20]	[20]	[18]
Seminiferous tubular atrophy, unilateral	0	1 (2.00)	2 (2.50)	1 (4.00)
Seminiferous tubular atrophy, bilateral	1 (2.00)	3 (1.67)	4 (1.75)	5 (1.80)
Total	1	4	6†	6 ‡
Males – Carcinogenicity study				
Epididymides [No. examined]	[59]	[59]	[60]	[59]
No spermatozoa	9	8	19‡	29**
Reduced no. spermatozoa	8 (2.25)	4 (2.25)	9 (1.78)	18* (2.72)
Abnormal spermatogenic cells in duct	20 (1.70)	12 (1.83)	29 (2.10)	46** (2.24)
Epithelial vacuolation in duct	10	11	16	23*
Intraepithelial lumina	8	7	13	27**
Testes	[60]	[60]	[60]	[60]
Seminiferous tubular atrophy, unilateral	23	15	15	7 ‡‡
Seminiferous tubular, atrophy, bilateral	12 (2.17)	6 (3.50)	17 (3.18)	41** (3.61)
Seminiferous tubular atrophy, total	35	21	32	48‡‡
Seminiferous tubular degeneration	0	1	3	4
Prostate	[60]	[59]	[60]	[60]
Acinar atrophy	1	2	1	4
Reduced colloid	1	4	10‡‡	7‡
Seminal vesicle [No. examined]	[60]	[60]	[60]	[59]
Atrophy	6	7	1	12
Females – Toxicity study – 52 weeks				
Pancreas [No. examined]	[20]	[0]	[0]	[20]
Focal acinar cell atrophy	0	0	0	7**
Pituitary [No. examined]	[20]	[5]	[4]	[20]
Hyperplasia, pars distalis	0	0	0	6*
Ovaries [No. examined]	[20]	[5]	[4]	[20]
No corpora lutea	2	2	2	8‡
Females – Carcinogenicity study				
Brain	[60]	[52]	[51]	[60]
Depression due to enlarged pituitary	26	34*	40**	43**
Ovaries	[60]	[50]	[49]	[60]
No corpora lutea	17	24*	26*	33**
Historical control incidence	Range = 40-64%; average = 57%			

Data taken from pages 37-41 (toxicity study for males) and Table 12 (pp. 176-186, 191-206, 218-240), MRID 46387811.
[a]Animals in the toxicity study that died before week 52 are excluded because data on severity of the lesions in animals dying early were not included in the text tables (pp 37-38).
[b]Average severity of affected animals: 1 = minimal, 2 = slight, 3 = moderate, 4 = marked
*p≤0.05, **p≤0.01; statistically significant, treated group compared with the control, reported by the study author
†p≤0.06; ‡p≤0.05, ‡‡p≤0.01, statistically, treated group compared with the control, calculated by the reviewer.

b. **Neoplastic:** Notable neoplastic lesions are presented in Table 8. Mid- and high-dose male rats had a significantly increased incidence of interstitial (Leydig) cell adenoma compared with control rats. The incidence at both doses exceeded the upper range of historical controls and is, therefore, considered treatment related. Pituitary pars distalis adenoma was found in all female groups including controls at the 52 week sacrifice. There was no treatment-related increase in the incidence in treated females. In the carcinogenicity phase, pituitary pars distalis adenoma was a common lesion in male rats with the incidence in the high-dose group slightly less than that of controls. The incidence of pituitary pars distalis adenoma was significantly increased in the mid-dose group females in the carcinogenicity study, and the incidence of par distalis adenoma and adenocarcinoma combined was significantly increased in mid- and high-dose group females compared with controls in the carcinogenicity phase. Pars distalis adenoma and adenoma/adenocarcinoma combined were very common in female rats occurring in 53% and 70%, respectively, of controls, 72% and 85%, respectively, of mid-dose group females, and 60% and 85%, respectively, of high-dose group females. The incidences of the adenocarcinoma in high-dose group females and combined lesions in mid- and high-dose groups were slightly greater than the upper range for historical controls; however, it is doubtful that these lesions are related to treatment with the test material.

TABLE 8. Neoplastic lesions in male and female rats fed LGC-30473 - carcinogenicity study

Organ/Lesion	Dietary concentration (ppm)			
	0	100	300	650
	Males			
Testes [No. examined]	[60]	[60]	[60]	[60]
Interstitial (Leydig) cell adenoma	1 (1.7)[a]	4 (6.7)	6* (10.0)	7* (11.7)
Historical controls	range = 0-6.2%; average = 2.5%			
Pituitary [No. examined]	[60]	[60]	[60]	[60]
Adenoma, pars distalis	26 (43)	24 (40)	22 (37)	22 (37)
Adenocarcinoma, pars distalis	2 (3)	1 (1.7)	2 (3)	0 (0)
adenoma + carcinoma	28 (47)	25 (42)	24 (40)	22 (37)
	Females			
Pituitary [No. examined]	[60]	[60]	[60]	[60]
Adenoma, pars distalis	32 (53)	39 (65)	43** (72)	36 (60)
Adenocarcinoma, pars distalis	10 (17)	9 (15)	8 (13)	15 (25)
Adenoma + adenocarcinoma, pars distalis	42 (70)	48 (80)	51* (85)	51* (85)
Historical controls				
adenoma	range = 56-70%;	average = 63%		
adenocarcinoma	range = 2-15%;	average = 10%		
adenoma + adenocarcinoma	range = 68-82%	average = 73%		

Data taken from pages 38-39 and Table 12 (pp.187-190 and 212-217). MRID 46387811.
[a]Numbers in parentheses are percent of affected animals in the group, calculated by the reviewer.
†$p \leq 0.06$, *$p \leq 0.05$, statistically significant, treated group compared with the control, calculated by the reviewer.

III. DISCUSSION and CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study author noted the reduction in weight gain during the first week of the study in high-dose rats of both sexes and mid-dose females was accompanied by only a small reduction in food consumption. The study author concluded that high-dose females reduced weight gain was not due to reduced food consumption as indicated by only a slight reduction in food efficiency. No treatment-related effects were observed during ophthalmoscopic examination, FOB, hematologic evaluation, or urinalysis. The study author attributed changes in serum cholesterol glucose, and globulin in male and female rats to a general increase in metabolic activity indicated by hepatocyte hypertrophy observed in a few rats in the toxicity study. The study author noted that the male reproductive organs are targets for the test material. Epididymal and seminal vesicle weights were reduced, macroscopic changes were observed in the testes and epididymides, and microscopic changes were observed in the testes and epididymides at the mid- and high-doses and in the prostate and seminal vesicles at the high-dose. Microscopic changes in the testes included both non-neoplastic lesions and neoplastic lesions in the mid- and high-dose groups. The study did not report any treatment-related histopathologic lesions in female rats. The study author concluded that the NOAEL for carcinogenic potential was 100 ppm for males and 650 ppm for females and the NOAEL for toxic potential was 100 ppm for males and 300 ppm for females.

B. **REVIEWER COMMENTS:** No treatment-related clinical signs, effects on survival/mortality, abnormalities of the eyes (ophthalmoscopic examination), hematologic changes, or urinalysis changes were observed in any group of male or female rats administered the test material. The number of rats surviving in each group was well within the requirement at 18 months and all groups met the minimal requirement at study termination. The FOB evaluation did not show any differences between treated and control rats that could be considered adverse or attributed to treatment with the test material. Fewer high-dose females vocalized during handling than controls, but no adverse effect can be attributed to this observation. Decreased hindlimb grip strength in high-dose males was observed after treatment for 32 weeks but not for 49 weeks; this finding is not considered treatment related.

The study author did not conduct a statistical analysis on mean body weight, but the data showed that mean body weights of all groups of males and the low- and mid-dose female groups were similar to those of controls throughout the study. Body weight gain was significantly decreased in mid- and high-dose males after treatment for 1 week; no treatment-related effect on weight gain was observed in males after week 1. Weight gain was significantly decreased in females at all dose levels after the first week of treatment, and weight gain by the high-dose group remained below that of controls for the remaining weeks of the study. Mid- and high-dose males and all treated groups of females consumed significantly less food than controls during the first week of treatment, but remained within 5% of control during the week 2-50 interval and for the entire study. Food efficiency showed only a slight decrease in high-dose males and females during week 1 of treatment and was similar to that of controls for the first 14 weeks, indicating that the effect on weight gain was not due to reduced food consumption.

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The significant changes in clinical chemistry parameters were not accompanied by histopathological correlates. The investigators attributed the small increase in protein (globulins primarily) in females during the first year of treatment to an increase in general metabolic activity. The reviewer agrees with the investigators and also notes that these changes are not considered adverse. The significant changes in electrolytes in male and female rats were not considered adverse because no pathological correlates were observed during the study.

Changes in organ weights and gross and histopathological findings indicated that the male reproductive organs were affected by treatment with the test material. These effects were first observed grossly and microscopically at 52 weeks. Epididymal weight was significantly decreased in mid- and high-dose group males and seminal vesicle weight was significantly decreased in high-dose group males compared with those of controls at study termination. Gross examination showed that the testes were small in the high-dose group and microscopic examination showed seminiferous tubular atrophy and abnormal spermatogenic cells in the epididymal duct in mid- and high-dose group male rats at 52 weeks. In the carcinogenicity phase, gross examination showed significantly increased incidences of small, blue, and flaccid testes and small and flaccid epididymides in high-dose group males. The incidence of testicular masses also was increased in mid- and high-dose group males. The masses corresponded with testicular neoplasms. Microscopic examination of the testes in male rats in the carcinogenicity phase showed significantly increased incidences of bilateral seminiferous tubular atrophy and significantly decreased incidence of unilateral seminiferous tubular atrophy at the high-dose level. These results suggest that the unilateral lesion was treatment-related and progressed to the more severe bilateral lesion. Microscopic examination of the epididymides of males in the carcinogenicity phase showed significantly increased incidences of epididymides with reduced number of spermatozoa in high-dose group males and significantly increased incidence of epididymides with absent spermatozoa at the mid- and high-dose groups. These findings showed progression from reduced spermatozoa to the more severe condition of absent spermatozoa in the epididymis. Other epididymal lesions in male rats organs included epithelial vacuolation in the epididymal duct, intraepithelial lumina in the epididymis, acinar atrophy and reduced colloid in the prostate, and atrophy in the seminal vesicles in the high-dose group. Although the incidences of acinar atrophy in the prostate and seminal vesicle atrophy were not significantly increased compared with control incidences, these lesions are considered treatment-related, because of the other reproductive organs affected.

In female rats, organ weight changes (kidneys and uterus+cervix) were not associated with histopathological changes and are not toxicologically significant. No statistically increased incidences of gross lesions were observed in females at 52 weeks. The significantly increased number of high-dose group females in the carcinogenicity phase with brain depression from a pituitary mass was associated with pituitary neoplasms. Microscopic examination of females at 52 weeks also showed increased incidences of focal acinar cell atrophy in the pancreas, pars distalis hyperplasia in the pituitary, and absence of corpora lutea in the ovaries of high-dose females. Pituitary hyperplasia was associated with the pituitary neoplasms. The pancreatic lesion was not observed in the carcinogenicity phase and is not considered treatment related. The report noted that the increased incidence of ovaries with absent corpora lutea was statistically significant at the low- and mid-dose levels although the ovaries

of all animals were not examined. The reviewer believes that a statistically analysis of this finding should not have been conducted on the low- and mid-dose groups because all animals were not examined at this site. The concurrent control incidence in this study was below the lower range of historical controls, which could have contributed to the statistical increase for the high-dose group. Therefore, the ovarian lesions are not considered treatment-related.

The LOAEL for males is 300 ppm (16.4 mg/kg bw/day) based on effects in male reproductive organs (testes, epididymides, prostate, and seminal vesicles) and the LOAEL for females is 650 ppm (45.5 mg/kg bw/day) based on decreased body weight and body weight gain. The NOAEL for males is 100 ppm (5.5 mg/kg bw/day) and the NOAEL for females is 300 ppm (21.0 mg/kg bw/day).

The incidence of testicular interstitial cell adenoma was significantly increased in males at the mid-and high-dose levels. A clear dose-related trend was not observed at the two highest doses; nevertheless, the neoplasms at both dose levels are considered treatment related, because the incidence of interstitial cell adenoma at both doses were above the upper range of historical controls. The test material produced non-neoplastic lesions in the testes, epididymides, seminal vesicles, and prostate and neoplastic lesions in the testes indicating that the mode of action of LGC-30473 is possibly endocrine disruption affecting the pituitary-gonadal axis in males.

In females, the increased incidence of pituitary pars distalis adenoma was significantly increased only at the mid-dose level, whereas the incidence of pars distalis adenoma/adenocarcinoma combined was increased in both mid- and high-dose group female rats. The incidences of pituitary adenoma in mid-dose group females, pituitary adenocarcinoma in high-dose group females, adenoma/adenocarcinoma combined in mid- and high-dose group females as well as the adenocarcinoma in control were greater than the upper range of historical controls. Nevertheless, it is doubtful that these lesions are treatment related, because the concurrent and historical control incidences are very high, affecting more than 70% of the animals.

The animals in this study were adequately dosed based on reduced body weight and weight gain in treated females compared with the controls and the induction of non-neoplastic lesions in the testes and epididymides in treated male rats.

Note: On February 15, 2006, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Ethaboxam. The CARC concluded (Memo, TXR No: 0054172) that there was a significant increasing trend, and a significant difference in pair-wise comparison of the 650 ppm dose group with the control for benign interstitial (Leydig) cell tumors of the testes, both at $p < 0.05$. It was also concluded that the pituitary tumors observed in female rats were not treatment-related.

C. **STUDY DEFICIENCIES:** The only noteworthy deficiency in this study was the lack of statistical analysis of the body weight data and the lack of weekly body weight gain data. These deficiencies did not affect the interpretation of the data.

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